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DOCUMENT-IDENTIFIER: US 5683715 A
TITLE: Taxane-containing phosphatidylcholine liposomes

Brief Summary Text (7):
This invention provides a liposome comprising a taxane and a bilayer comprising a lipid, wherein the lipid consists essentially of a phosphatidylcholine. Typically, the concentration of the taxane is at least about one mole percent, preferably from about 1 mole percent to about 4 mole percent. The taxane can be paclitaxel, taxotere, a baccatin or a cephalomannine, and is preferably paclitaxel. Preferably, the taxane is associated with the liposomal bilayer. The phosphatidylcholine (PC) is an unsaturated or partially unsaturated PC and includes, without limitation, dioleoyl phosphatidylcholine (DOPC), palmitoyloleoyl phosphatidylcholine (POPC), or egg phosphatidylcholine (EPC); preferably, the PC is EPC. Preferably, the liposome is unilamellar, more preferably a unilamellar liposome having an average diameter of from about 100 nm to about 200 nm. The liposome can be dehydrated.

Drawing Description Text (2):
FIG. 1. Gaussian analysis of the size distribution of EPC multilamellar liposomes having substantially equal interlamellar solute distribution (no paclitaxel). Run time: 5 min, 39 sec; average count rate: 340.3 kHz; channel width: 21.0 .mu.sec; temp.: 23 deg. C.; viscosity: 0.9325 centipoise; index of refraction: 1.333; print AT data: 500 kcounts; number of printouts: 10. Mean diameter: 204.5 nm; standard deviation: 75.1 nm (26.8%); chi squared: 0.2; baseline adjust: 0.00%; data: 508.2 k.

Drawing Description Text (3):
FIG. 2. Gaussian analysis of the size distribution of EPC SPLVs containing paclitaxel. Run time: 6 min, 25 sec; average count rate: 345.5 kHz; channel width: 26.0 .mu.sec; temp.: 23 deg. C.; viscosity: 0.9325 centipoise; index of refraction: 1.333; print AT data: 500 kcounts; number of printouts: 10. Mean diameter: 209.8 nm; standard deviation: 187.2 nm (60.4%); chi squared: 4.8; baseline adjust: 0.01%; data: 698.4 k.

Drawing Description Text (4):
FIG. 3. Gaussian analysis of the size distribution of EPC/paclitaxel unilamellar liposomes produced by extrusion of SPLVs through polycarbonate filters with 0.1 micron pores (LUVET 100s). Run time: 8 min, 42 sec; average count rate: 356.5 kHz; channel width: 12.0 .mu.sec; temp.: 23 deg. C.; viscosity: 0.9325 centipoise; index of refraction: 1.333; print AT data; 500 knouts; number of printouts: 10. Mean diameter: 105.2 nm; standard deviation: 22.3 nm (21.2%); chi squared: 0.3; baseline adjust: 0.08%; data: 503.6 k.

Drawing Description Text (5):
FIG. 4. Gaussian analysis of the size distribution of EPC/paclitaxel unilamellar liposomes produced by extrusion of SPLVs through polycarbonate filters with 0.2 micron pores (LUVET 200s). Run time: 8 min, 42 sec; average count rate: 345.9 kHz; channel width: 16.0 .mu.sec; temp.: 23 deg. C.; viscosity: 0.9325 centipoise; index of refraction: 1.333; print AT data: 500 kcounts; number of printouts: 10. Mean diameter: 160.8 nm; standard deviation: 47.0 nm (29.2%); chi squared: 0.3; baseline adjust: 0.00%; data: 624.8 k.

Detailed Description Text (8):
Liposomes can be unilamellar, that is, have a single lipid bilayer, or multilamellar,

having multiple lipid bilayers, and can have diameters ranging from about 25 nm to several microns. Multilamellar liposomes (MLVs) comprise a plurality of lipid bilayers each of which encloses an aqueous compartment; preferred MLVs have aqueous compartments comprising a solute, wherein the concentration of the solute in each of the aqueous compartments is substantially equal, i.e., the liposome has substantially equal interlamellar solute distribution. Preferably, the liposome of this invention is unilamellar, more preferably a unilamellar liposome having an average diameter of from about 100 nm to about 200 nm. For example, this unilamellar liposome can be a LUVET.sub.100 or LUVET.sub.200, i.e., a unilamellar liposome produced by extrusion of multilamellar liposome through filters with pore sizes of 100 nm or 200 nm, respectively (see Cullis et al., U.S. Pat. No. 5,008,050, the contents of which are incorporated herein by reference).

Detailed Description Text (10):
Liposomal dehydration generally requires use of a hydrophilic drying protectant (see U.S. Pat. No. 4,880,635, the contents of which are incorporated herein by reference). This hydrophilic compound is generally believed to prevent the rearrangement of the lipids in the liposome, so that the size and contents are maintained during the drying procedure and through rehydration, such that the liposomes can be reconstituted. Appropriate qualities for such drying protectants are that they be strong hydrogen bond formers, and possess stereochemical features that preserve the intramolecular spacing of the liposome bilayer components. Saccharide sugars, preferentially mono- and disaccharides, more preferably, disaccharides, are suitable drying protectants for liposomes. Alternatively, the drying protectant can be omitted if the liposome preparation is not frozen prior to dehydration, and sufficient water remains in the preparation subsequent to dehydration and if the liposome is multilamellar. Preferably, the protective sugar concentration in the liposome composition prior to dehydration is from about 100 mM to about 250 mM, or from about 5 moles of sugar per mole of phosphatidylcholine to about 12.5 moles of sugar per mole phosphatidylcholine. The protective sugar should be present at both inside and outside the liposome bilayers prior to dehydration. Without intending to be limited by theory, it is generally believed that protective sugars inside liposome bilayers prior to dehydration inhibit leakage of liposome contents, and that outisde sugars inhibit interliposomal aggregation and fusion. Further provided herein is a liposome composition comprising: (I) a dehydrated liposome which comprises a taxane and a bilayer comprising a lipid; and (ii) one or more protective sugars at the inside and outside surfaces of the bilayer, wherein the lipid consists essentially of a phosphatidylcholine

Detailed Description Text (11):
A variety of methods exist for producing liposomes (for a review, see, e.g., Szoka and Paphadjopoulos, in: Liposomes: From Physical Structure to Therapeutic Applications (C. G. Knight, ed., Elsevier/North Holland, pp. 51-82 (1981); Cullis et al., in: Liposomes, From Biophysics to Therapeutics M. J. Ostro, ed.), Marcel Dekker, pp. 39-72 (1987)). Bangham's original preparation (J. Mol. Biol. 13:238 (1965)) involves suspending phospholipids in an organic solution and then evaporating the solution to dryness, leaving a phospholipid film on the walls of the reaction vessel. Next, an appropriate amount of a chosen aqueous medium is added; the resulting liposomes, which consist of multilamellar vesicles (MLVs), are dispersed by mechanical means. This technique provided the basis for the development of sonicated unilamellar vesicles by Paphadjopoulos et al. (Biochem. Biophys. Acta. 135:624 (1968)), Lenk et al. (U.S. Pat. Nos. 4,522,803, 5,030,453 and 5,169,637) and Fountain et al. (U.S. Pat. No. 4,588,708) disclose methods for producing multilamellar liposomes with substantially equal interlamellar solute distribution. FATMLVs, freeze-and-thaw multilamellar vesicles, also have substantially equal interlamellar solute distribution (Cullis et al., U.S. Pat. No. 4,975,282). These vesicles are produced by first dispersing a lipid in an aqueous solvent to form multilamellar liposomes. The resulting lipid vesicles are rapidly frozen, the frozen mixture is warmed, and then the freeze-thaw cycle is repeated at least three times. Furthermore, Janoff et al. (U.S. Pat. No. 4,721,612) and Bolcsak et al. (U.S. Pat. No. 5,100,662) describe the preparation of liposomes of enhanced stability using sterols. Cullis et al. (U.S. Pat. No. 5,008,050) and Loughrey et al. (U.S. Pat. No. 5,059,421 ) disclose the preparation of a population of liposomes with a defined size distribution by extrusion of liposomes through filters under pressure. The contents of these patents are incorporated herein by reference.

Detailed Description Text (13):
Also provided is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the liposome. For the purposes of this invention, a "pharmaceutically acceptable carrier" means any of the standard carriers, diluents, excipients and the like generally intended for use in connection with the administration of biologically active agents to animals. Such carriers are well known in the art and are generally chosen with regards to a number of factors, such as the particular drug being used and the intended route of administration, which are understood by the ordinarily skilled artisan. Pharmaceutical carriers preferred for use in accordance with the practice of this invention are those well known carriers suitable for use in connection with intravenous administration of liposomes and include, but are not limited to, sterile aqueous solutions such as physiological saline, 5% dextrose USP solutions and various aqueous buffers, e.g., aqueous phosphate buffers. The total solute concentration in such carriers should be controlled to keep the composition isotonic. Pharmaceutically acceptable carriers may also contain additional components, such as anti-oxidants, preservatives and the like, which are compatible with the active agent. The choice of such additional components is well within the purview of the ordinarily skilled artisan. Other carriers, e.g., tablets for oral administration and oils for mucosal or topical administration, may be prepared employing general knowledge and used in accordance with the practice of this invention.

Current US Original Classification (1):
424/450